GUIDANCE FOR IDENTIFYING PESTICIDE CHEMICALS THAT HAVE A COMMON MECHANISM OF TOXICITY, FOR USE IN ASSESSING THE CUMULATIVE TOXIC EFFECTS OF PESTICIDES

I. INTRODUCTION

Pesticides are regulated under two major federal statutes: the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). These statutes were enacted in part to prevent unreasonable adverse effects on human health or the environment that may be caused by pesticides, especially those intended to be used for agricultural purposes. FIFRA requires substances that will be sold or distributed for use as pesticides to be registered with the Environmental Protection Agency (EPA). The Federal Food, Drug, and Cosmetic Act (FFDCA) requires EPA to set tolerance levels for pesticide residues in or on raw agricultural commodities or processed foods. A tolerance for a given pesticide residue represents the maximum legally allowable concentration of the pesticide residue that can be present in a raw agricultural commodity or processed food.

As part of its process to establish pesticide tolerances and register pesticides, the Agency (EPA) must make a determination of safety as to the general public: i.e., be reasonably certain that use of a given pesticide or consumption of raw agricultural commodities or processed foods that contain the pesticide and its residues will cause no harm to human health or the environment. A determination of safety is based on the assessed risks posed by the pesticide. Following risk characterization, EPA prescribes labeling and other regulatory requirements to ensure that use of the pesticide does not lead to exposures to the pesticide[1] that would be unsafe.

Historically, when determining the safety of a given pesticide, the assessment of risks to human health were generally based on the potential for the pesticide to cause a specific toxic effect(s) solely from exposure to the pesticide. In 1996 the Food Quality Protection Act (FQPA) was passed by Congress to amend FIFRA and FFDCA. FQPA requires EPA to periodically reassess all pesticide tolerances, and to consider additional factors when determining the safety of pesticides[2]. The Act specifically stipulates that

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1 In this document exposure to a pesticide includes the pesticide and any or all of its residues.

2 For specific details see *The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Federal Food, Drug, and Cosmetic Act (FFDCA) As Amended by the Food Quality Protection Act (FQPA) of August 3, 1996;* U.S. Environmental Protection Agency, Office of Pesticide Programs, document # 730L97001, March, 1997.

when determining the safety of a pesticide[3] EPA must consider, among other factors[4], aggregate (i.e., total dietary, residential, and other non-occupational) exposure to the pesticide and the possibility of cumulative toxic effects to human health that may result from concomitant dietary or residential exposure to other pesticides that are toxic from a common mechanism. Hence, in assessing the risks posed by a given pesticide, EPA must assess the combined risks to human health that can result from exposure to the pesticide and other pesticides that are toxic from a common mechanism[5].

In order to assess the cumulative effects from concomitant exposure to pesticides that are toxic from a common mechanism, the Agency needs to identify and categorize pesticides that are toxic from a common mechanism. The primary purpose of this document is to describe the approach that EPA will use for identifying and categorizing pesticide chemical substances that have common mechanisms of toxicity. Specifically, this document describes:

- EPA's interpretation of common mechanism of toxicity with respect to making a determination of safety under FFDCA as amended by FQPA;
- the specific steps that need to be taken for identifying, inferring or refuting a common mechanism of toxicity;
- the types of data (and their sources) that are needed for doing so;
- how these data are to be used in making decisions regarding common mechanisms of toxicity;
- factors that will be considered when conducting combined risk assessments that characterize whether or not cumulative toxic effects can reasonably be expected to occur following exposure to two or more pesticide substances that

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3 FFDCA as amended by FQPA requires that when establishing or re-evaluating a tolerance for a pesticide residue the Agency must determine that the tolerance is safe. As stated in FFDCA, the term "safe" with respect to a tolerance for a pesticide residue means that the Agency has determined that there is reasonable certainty that no harm will result from aggregate exposure to the pesticide. See reference cited in footnote 2 for additional details.

4 For a description of these factors, see the reference cited in footnote 2.

5 It is also possible that cumulative toxicity may result from concomitant exposure to pesticides that have different mechanisms of toxicity. This document deals only with the cumulative toxicity that may result from concomitant exposure to pesticides that have a common mechanism of toxicity.

are toxic from a common mechanism.

Detailed discussions on the use of common mechanisms of toxicity when making determinations of safety or on the approaches the Agency will use for assessing cumulative toxic effects are not provided here. These will be presented at a later date.

II. DEFINITIONS OF SPECIFIC TERMS USED IN THIS NOTICE

A number of terms are critical to discussions of common mechanism of toxicity, and are used in this document. These terms [6] are defined and discussed here to clarify EPA's position in making decisions regarding common mechanisms of toxicity and in the use of data needed for combined risk assessments that characterize cumulative toxicity.

Toxic Effect. A toxic effect is an effect observed in humans that results from exposure to a chemical substance and that will or can reasonably be expected to endanger or adversely affect quality of life. Some examples of toxic effects are acute lethality, loss of hearing, renal tubule necrosis and cardiomyopathy, to name just a few.[7] It is the policy of EPA to assume that substances known to cause toxic effects in experimental animals will cause the same effects in humans, unless data to the contrary are available.

Common Toxic Effect. Two or more pesticide chemicals that are known to cause the same adverse (toxic) effect in the same organ or tissue are said to cause a common toxic effect. Thus, a toxic effect observed in studies involving animals or humans exposed to a pesticide chemical is considered common with a toxic effect caused by another chemical if there is concordance with both site and nature of the effect.

Toxicophore. Substances that are capable of causing a toxic effect contain a structural feature or moiety that bestows the toxic property. This structural feature or moiety is referred to generically as the toxicophore. A toxic substance elicits its toxicity through interaction of its toxicophore with a biomolecular site (receptor)[8] in cells of tissue or organs to cause changes or alterations in normal cellular biochemistry. These

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6 None of these terms are defined (some are not mentioned) in FFDCA as amended by FQPA.

7 Toxic effect is not synonymous with toxic endpoint. Toxic endpoint is a quantitative measure of a toxic effect. For example, acute lethality is a toxic effect, an LD_{50} value (median lethal dose) is the toxic endpoint that pertains to the effect.

8 A biomolecular site or receptor refers to a specific area on a particular type of biomolecule (e.g, DNA, RNA, peptide, protein, lipoprotein, enzyme, etc.) within a cell. The toxicophoric portion of a given pesticide may interact reversibly or irreversibly with its biomolecular site, depending upon the reactive nature of the toxicophore and the biomolecular site.

biochemical changes or alterations lead to disruption of the physiological process(es) the tissue or organs perform and, ultimately, the toxic effect. With many toxic substances, the toxicophore does not interact directly with its biomolecular sites; it undergoes metabolic conversion (bioactivation) to a metabolite that interacts with the biomolecular site.

Substances that contain the same toxicophore may cause a common toxic effect (i.e., the same toxic effect within the same organ system or area of the body). This is particularly likely with substances that are very similar in structure. With some substances that contain the same toxicophore, however, the nature of the toxic effect caused by each substance is the same, but the organ or specific location in the body where the effect occurs may differ among the substances. It is also possible for two substances that contain the same toxicophore to cause entirely different toxic effects. Differences between location or nature of a toxic effect among substances containing the same toxicophore can be ascribed to the specific structural and physicochemical differences between the substances, and the affect these differences have on their respective pharmacokinetics (i.e., absorption, distribution, metabolism, and excretion of each substance) and on the interaction of the toxicophore with biomolecular sites.

Mechanism of Toxicity.[9] For the purpose of implementation of FFDCA as amended by FQPA, mechanism of toxicity is defined as the major steps leading to an adverse health effect following interaction of a pesticide with biomolecular sites. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction that are required in being able to describe a mechanism of toxicity. Generally, the more that is understood about the various steps in the pathway leading to an adverse effect, the more confident one is about the mechanism of toxicity. For instance, a mechanism of toxicity may be described by knowing the cascade of effects such as the following: a chemical binds to a given biomolecular site *in vitro,* and causes the receptor- related molecular response; *in vivo* it also leads to the molecular response and causes a number of intervening biological and morphological steps that result in an adverse effect. Other processes may describe a mechanism of toxicity in other cases.

Common Mechanism of Toxicity. For the purpose of implementation of FFDCA as amended by FQPA, common mechanism of toxicity pertains to two or more pesticide chemicals that produce an adverse effect(s) to human health by the same, or essentially the same, sequence of major biochemical events. Hence, the underlying basis of the toxicity is the same, or essentially the same, for each chemical.

Cumulative Toxic Effects. Concurrent exposure to two (or more) chemical substances may result in an enhancement or diminution of one or more of the toxic

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9 In the context of this document mechanism of toxicity refers to the mechanism by which a pesticide substance is toxic to humans or experimental animals, and not the mechanism by which it is toxic to target or intended species (i.e., its mechanism of pesticidal action). With some pesticides, however, the mechanism responsible for causing toxicity to humans or experimental animals is similar to the mechanism of pesticidal action.

effects caused by any of the substances alone. It is also possible that concurrent exposure may result in no change in the toxic effects caused by the chemicals alone. In some instances, concurrent exposure may result in a toxic effect that is not observed from exposure to any of the substances alone. Cumulative toxic effects are situations in which concommitant exposure to two or more chemical substances results in an overall increase in toxicity relative to the toxicity that is caused from exposure to any of the substances alone. The nature of the cumulative effect(s) is often identical or similar to an effect caused by one or more of the substances. The magnitude of the increase in the effect, however, may be: equal to (i.e., additive); greater than (i.e., synergistic, potentiated); or less than that expected by addition of the individual toxic responses caused by each substance.

There are a variety of ways in which chemical substances can cause cumulative toxicity. Concurrent exposure to substances that cause a common toxic effect by a common mechanism of toxicity, for example, may result in cumulative toxicity. This is because the substances interact with the same biomolecular sites that cause the toxicity, and concurrent exposure is expected to result in additional interaction with more of the biomolecular sites and, hence, increased toxicity. Alternatively, a substance may enhance the toxicity of another substance by altering its pharmacokinetics (i.e., its absorption, distribution, metabolism or excretion). For example if the primary route of elimination of a toxic substance is via the kidney, its toxicity is likely to be enhanced from concomitant exposure to another substance that decreases renal function. Or, if the metabolism of a toxic substance serves to reduce its toxicity, the toxicity is likely to be enhanced from exposure to another substance that slows or prevents the metabolism.

For the purpose of implementation of FFDCA as amended by FQPA, cumulative toxic effects are the total anticipated toxicity resulting from concurrent exposure to two or more pesticide chemicals that are toxic from a common mechanism. While it is possible that cumulative toxicity may result from concomitant exposure to pesticides that have different mechanisms of toxicity, this document deals only with the cumulative effects that may result from concomitant exposure to pesticides that have a common mechanism of toxicity.

Structure-Activity Relationships. As discussed above, substances that contain the same toxicophore are likely to cause common toxic effects. However, the relative potency among the substances in their ability to cause the toxic effect may vary substantially. Relative potency is directly related to the specific or incremental structural differences between the substances and the influence these differences have on the ability of the toxicophore to reach or interact with its biomolecular site of action. The ability of two or more structurally-related substances to cause a common toxic effect and the influence that their structural differences have on toxic potency are referred to as structure-activity[10] relationships.

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10 In the context of this document the term "activity" is synonymous with toxicity.

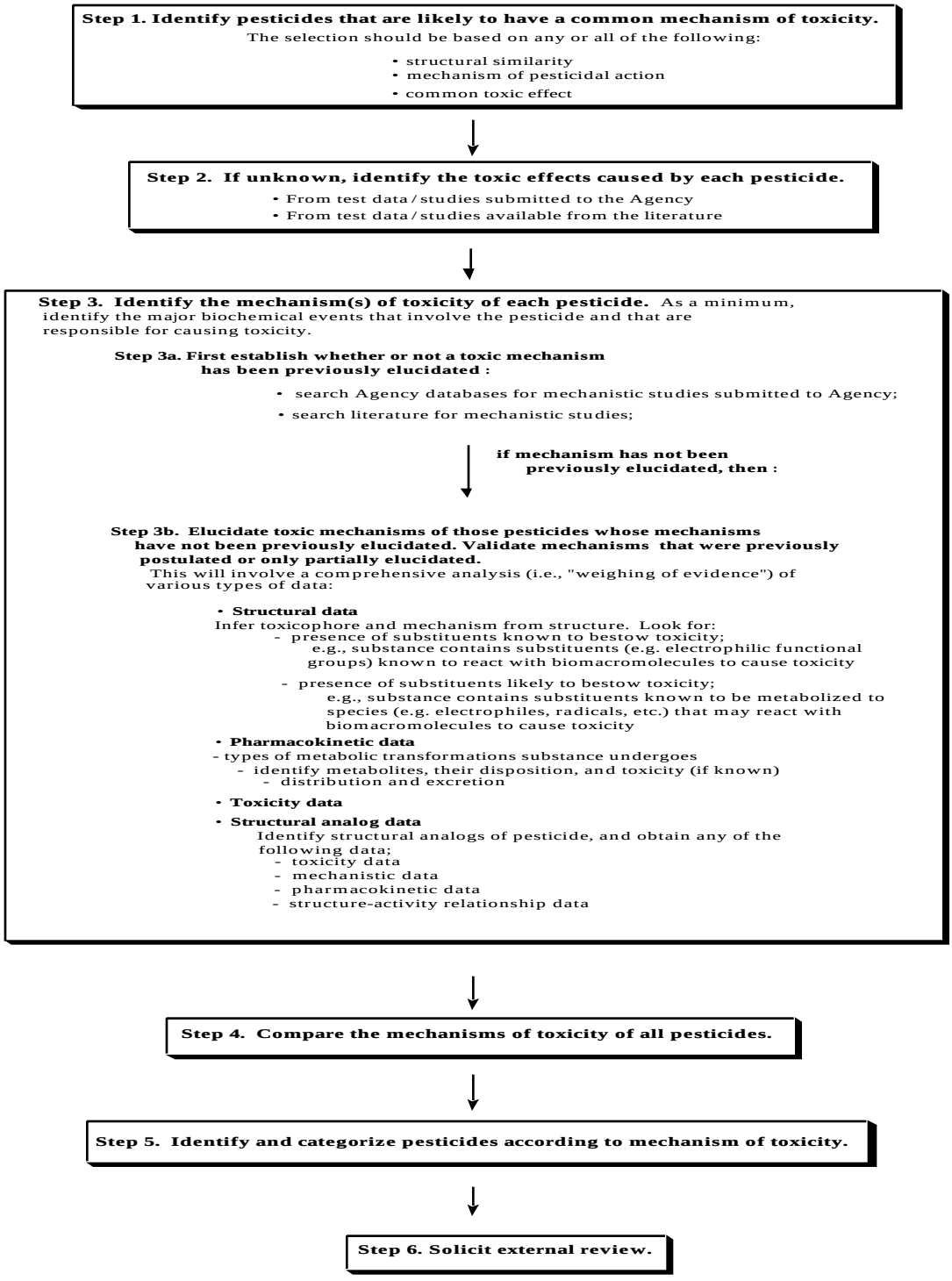
Relationships between structure and toxicity within a given series of structurally-similar substances or of a single given substance are often discernable from an analysis of the general structure, the chemical properties of the substance(s), information pertaining to the pharmacokinetics and toxicity of the substance(s) and, in the case of a series of analogous substances, the structural differences within the series and their corresponding affect on toxic potency. While knowledge of the mechanism of toxicity is usually not necessary to discern a causal relationship between structure and activity (toxicity), the relationship becomes more apparent and more useful when the mechanism of toxicity is known. Once deduced, the structure-activity relationship of the substance or the series can be useful for inferring the likelihood of an analogous, untested chemical causing the same toxicological effect, and for estimating its toxic potency. In cases where the mechanism of toxicity is known for a substance or a group of substances, structure-activity relationships are useful for inferring the mechanism of toxicity of an analogous, untested substance and for supporting or refuting proposed mechanisms of toxicity of analogous untested substances. An example of a pesticide chemical class with well established structure-activity relationships and in which mechanism of toxicity has been elucidated is the ethylene-bisdithiocarbamate class: many of these substances are metabolized in the body to ethylene thiourea and cause hypothyroidism.

III. IDENTIFYING PESTICIDE CHEMICALS THAT ARE TOXIC FROM A COMMON MECHANISM.

To assess the combined risks and cumulative toxicity of pesticides that are toxic from a common mechanism, EPA will need to identify those pesticides that are toxic from a common mechanism. In order to identify pesticides that are toxic from a common mechanism, EPA will first identify the mechanisms by which individual pesticides are toxic, and then group them in accordance to commonality of toxic mechanism and effect. Once grouped, combined risk assessments can be performed and the cumulative toxic effects that may result from concomitant exposure to pesticides within a group can be evaluated.

The conceptual framework of the process that EPA will use to identify pesticide chemicals that are toxic from a common mechanism is illustrated in Figure 1 and described below. This process is designed to enable EPA to make accurate identification and categorization of pesticides that are toxic from a common mechanism, in both a timely and resource-effective manner. (Specific examples of the application of this process are in preparation, and will be made available at a future date.) To implement the process the Agency has covened an in-house multidisciplinary team of scientists who are experts in chemistry, biology, pharmacology, toxicology, and pharmacokinetics. It is the responsibility of this team to identify and

Figure 1. Process for Identifying Chemicals that are Toxic from a Common Mechanism



analyze data and information pertaining to toxic mechanisms, and to utilize expert judgement in making decisions regarding mechanisms of toxicity of pesticides. The following policies and practices will be used by the Agency for identifying chemicals that have a common mechanism of toxicity:

- A thorough identification and analysis of all relevant information will be undertaken for each pesticide chemical under consideration. This will provide the basis for identifying underlying mechanisms of toxicity;

- Sound scientific judgement and current toxicologic theory will be applied to available data to make reasonable, scientifically valid decisions;

- A weight-of evidence approach will be used to support the development of hypotheses pertaining to specific or common mechanisms of toxicity. Generally, no single piece of information will suffice to support the characterization of a specific or common mechanism of toxicity: this finding will be supported by the analysis and inter-relationships of many pieces of information;

- External review of EPA's decisions concerning: ulitilization of established toxic mechanisms; identification of toxic mechanisms for specific pesticides; and grouping of pesticides by mechanism of toxicity, will be solicited.

IIIa. Selection of Pesticides that are likely to have a Common Mechanism of Toxicity (Step 1).

The process of identifying pesticides that are toxic from a common mechanism begins with a preliminary grouping of chemicals that are likely to have a common mechanism of toxicity (step 1, Figure 1). Substances that are related structurally, or have a similar mechanism of pesticidal action, or produce the same toxic effects in humans or experimental animals are those that are most likely to cause toxicity by a common mechanism. Hence, initial grouping of pesticides will be based upon at least one one of the following criteria:

- structural similarity;
- mechanism of pesticidal action;
- common toxic effect.

Use of structural similarity as a starting point for grouping chemicals relies on the assumption that substances that are structurally analogous contain the same toxicophore and interact similarly with their cellular biomolecular sites in causing toxicity. Thus, their mechanisms of toxicity are likely to be the same. Search queries for identification of structurally similar pesticides may include, for example: toxicophore (if known); base structure; and accompanying alkyl groups, functional groups or other substituents that may impact on the propensity of a substance to produce a toxicological response common with those of analogous chemicals.

Grouping of pesticides based on pesticidal mode of action is justifiable because the mechanisms by which a number of pesticides are toxic to humans are fundamentally similar or, in some cases, identical to their mechanisms of intended toxicity to pests. With such pesticides the portion of the molecule that is responsible for pesticidal action is also responsible for human toxicity (i.e., the portion of the molecule that bestows pesticidal activity is also the toxicophore). The pesticidal action and human toxicity of these pesticides are often due to analogous interactions of their toxicophores with specific biomolecular sites that are common to pests and humans, respectively.

Grouping of pesticides by common toxic effect known to occur in experimental animals or humans is based on the possibilty that commonality in toxicity among two or more pesticides could be due to a common mechanism. Since this type of grouping is functionally-based, not structure-based, it enables the identification of structurally un-related pesticides that are toxic from a common mechanism that otherwise may not be identifiable from groupings based on structural similarity or mode of pesticidal action alone.

Not all common toxic effects can be used as a preliminary basis for grouping substances. Common toxic effects which have many possible unrelated etiologies, or which could be defined as nonspecific in origin are not appropriate as the primary basis for initial grouping of chemicals. These effects, such as body weight changes or death for example, can result from many unrelated factors and are usually of limited value in understanding mechanism of toxicity. Therefore, they will not be used as a basis for initial grouping of pesticides. An exception, however, is genetic alterations. While genetic alterations can result from a variety of causes, knowledge of the mechanism by which a chemical substance causes genetic alterations can provide insight into the mechanism by which it causes adverse human health effects. Therefore, data for chemicals with common mutagenic effects may serve as a basis for initial grouping of such chemicals.

Although structural similarity, common mechanism of pesticidal action, and the occurrence of a common toxic effect will be used as factors for initial grouping of pesticides, a decision as to whether substances identified under step 1 have a common mechanism of toxicity will require further examination and validation. As shown in the remaining steps of Figure 1, examination and validation will involve scientifically defensible identification of the mechanism of toxicity of each pesticide, and subsequent comparison of each mechanism to confirm or rule-out commonality.

IIIb. Identification of the Toxic Effects Caused by each Pesticide Chemical (Step 2).

Following the preliminary grouping of pesticides (step 1, Figure 1), the toxicological effects of greatest concern will be characterized for each pesticide. These effects will be used during the identification of toxic mechanisms (step 3) and in assessing cumulative effects of pesticides that are toxic from a common mechanism. EPA has previously established the principle toxic effects of many pesticides. A detailed evaluation of available toxicology data will be undertaken to identify the toxic effects of most concern for pesticides whose principle toxic effects have not yet been fully established, or need to be re-evaluated. Evaluation of data from toxicology studies will be pivotal to making determinations of which toxic effects are of most concern for a given pesticide. The primary data set used by EPA will be toxicity data generated in support of regulatory activities as outlined in 40 CFR 158. The Agency may also use toxicity data obtained from other studies, such as those in the published literature. The evaluation of toxicology data for purposes of identifying toxic effects will be conducted in a manner similar to that used by EPA in their pesticide registration and re-registration programs.

IIIc. Identification of the Toxic Mechanism(s) of each Pesticide Chemical (Step 3).

In order to determine whether or not pesticides identified under step 1 (Figure 1) are toxic from a common mechanism, the biochemical events by which each pesticide causes its principle toxic effect(s) will need to be identified and compared to the other pesticides. Generally, the more that is understood about the various biochemical events that lead to a toxic effect, the more apparent and scientifically acceptable is the mechanism of toxicity. While desirable, all of the specific biochemical events involving a pesticide in the causation of its toxicity do not need to be known or completely characterized in order to describe its mechanism of toxicity. What is needed, as a minimum, is an understanding of those biochemical events that are most crucial in causing the toxicity. Once the critical biochemical events pertaining to toxicity are understood for each pesticide, they can be compared and identification of those pesticides that are toxic from a common mechanism can be made.

The toxic mechanisms of some classes of pesticides have been characterized, and are described in various literature sources (e.g., textbooks, journals, etc.). These mechanisms were elucidated from the development and comprehensive analysis of data pertaining to the structure, pharmacokinetics and toxicity of the pesticides and their analogs. The toxicophoric moieties and structure-activity relationships of many of these pesticide classes were similarly characterized. The toxic mechanisms, toxicophores and structure-activity relationships of other pesticides, however, have not been fully characterized: either because of insufficient data, or the data needed to do so are available but have not yet been fully analyzed.

For the purpose of implementation of FFDCA as amended by FQPA, EPA will use previously established toxic mechanisms in the assessment of the combined risks and cumulative toxicity of pesticides that are toxic from a common mechanism, provided

that such mechanisms are consistent with current toxicological theory and deemed scientifically valid by the Agency to be used for these purposes. Hence, identification of toxic mechanisms will involve an initial search of Agency databases and the literature (step 3a, Figure 1) for studies that describe mechanisms of toxicity for any of the pesticides grouped under step 1. As shown in the Figure, the types of literature sources that will be searched and used include: standard reference and text books; peer-reviewed journals; government reports; and studies submitted to the Agency. This will allow segregation of the pesticides into two sub-groups: those whose mechanisms of toxicity are known; and those whose mechanism of toxicity are not known. Previously established mechanisms will be evaluated by the Agency to ensure that the mechanisms are consistent with current toxicological theory. When deemed necessary, more comprehensive literature or Agency database searches will need to be conducted to identify data that support or invalidate previously reported mechanisms of toxicity for which uncertainty exists.

EPA will attempt to elucidate or at least infer the mechanisms of toxicity of those pesticides whose toxic mechanisms are not known or not well understood, or for which there is an absence of direct mechanistic data. The elucidation or inference of a toxic mechanism will be based upon an evaluation of various data elements. The types of data and information that the Agency will use to develop a scientifically defensible characterization or inference of a given pesticide's toxic mechanism are: structural data; pharmacokinetic data; and toxicity data. In situations in which such data are not available or are insufficient for a pesticide, the Agency will use mechanistic, structural, pharmacokinetic or toxicity data pertaining to one or more analogs of the pesticide as a basis for elucidating the toxic mechanism of the pesticide. Identifying and obtaining pesticide or analog data will involve a comprehensive search of the literature and Agency databases. A primary source of these data and information will be studies that have been submitted to the Agency in support of registration and re-registration decisions and actions. Other sources of data will include peer-reviewed journals, text books, and government reports.

The Agency will analyze these data and, using a weight-of-evidence approach, will attempt to characterize or at least infer the major biochemical events involving a pesticide that are most critical in causing its toxicity (step 3b). From an analysis of a pesticide's structure, for example, the recognition of moieties that are known or expected to react with biological macromolecules, or are known or expected to be metabolized to reactive (e.g., radical, electrophilic) intermediates, or are otherwise known or expected to bestow toxicity may allow one to infer one or more biochemical events that are responsible for the substance's toxicity. Data that define the metabolism, distribution and excretion of a pesticide in the body are also very useful for establishing or inferring its mechanism of toxicity. Metabolism data that show the formation of toxic metabolites *in vivo* are especially useful for characterizing metabolic pathways which may be operative in causing toxic effects. Distribution and excretion data show the partitioning patterns of a substance in the body, and can be used to infer the types of various metabolic transformations that are most likely to occur and where they are most likely to take place. These data, in conjunction with structural and toxicity data, may also provide explanations for differences in toxicity of structurally

similar substances. Toxicity data can be helpful for inferring or supporting a toxic mechanism in many ways. Genetic alterations, for example, are important in the etiology of cancers and developmental effects. Genotoxicity tests (e.g., DNA binding, unscheduled DNA synthesis, or sister chromatid exchange assays) that show that a pesticide (or a metabolite thereof) forms a covalent adduct with DNA may be useful to infer or support a mechanism by which a pesticide known to cause cancer or developmental toxicity causes either of these effects.

Data pertaining to analogs of a pesticide will be used as surrogate data in situations in which such data are not available for the pesticide. An established mechanism of toxicity of a pesticide's analog(s), for example, may serve as a basis for inferring the toxic mechanism of the pesticide. Inferences based on the toxic mechanisms of an analog or analogs will only be made when: there is evidence that shows that the toxicological effects caused by the pesticide and the analogs are common; there is sufficient evidence that supports the toxic mechanism of the analog(s); and there is sufficient evidence for the Agency to conclude that the mechanism of toxicity of the pesticide is common with the mechanism of toxicity of the analog(s). Pharmacokinetic, toxicity, and structure-activity relationship data that are available for analogs of a pesticide will also be used as a basis for elucidating or inferring the toxic mechanism of the pesticide (step 3b, Figure 1). Results from genotoxicity tests, for instance, may be useful to infer or support a mechanism of a pesticide known to cause cancer or developmental toxicity. Genotoxicity data available for analogs of a pesticide known to cause cancer or developmental toxicity may be useful for inferring the mechanism by which the pesticide causes these effects. Genotoxicity profiles that are similar among a pesticide and its analogs are also useful in a weight-of-evidence confirmation of the suitableness of such inferences, particularly when mechanistic data are available for the analog and not the subject pesticide.

IIId. Comparison of Mechanisms of Toxicity: Identification and Categorization of Chemicals that are Toxic from a Common Mechanism (Steps 4 and 5).

Once the mechanism of toxicity of each pesticide has been identified, comparisons of mechanisms will be made to determine which pesticides are toxic from a common mechanism. Determinations that two or more pesticides are toxic by a common mechanism will be based on similarities in both the nature and sequence of the major biochemical events that cause toxicity. Mechanistic similarities that would support a finding of a common toxic mechanism include, for example, analogous interactions of the pesticides with identical or similar biomolecular sites or biomolecules, or the occurence of similar metabolic transformations that yield common or structurally analogous metabolites that interact with similar biomolecular sites or biomolecules, or that are otherwise involved in causing toxicity.

IIIe. External Review (Step 6).

External peer review of EPA's decisions concerning: ulitilization of established toxic

mechanisms; identification of toxic mechanisms for specific pesticides; and grouping (or non-grouping) of pesticides by mechanism of toxicity, will be solicited. Such review will provide additional evaluation to further ensure that Agency decisions are consistent, well-reasoned and reflect current scientific thinking.

IV. POLICIES FOR ASSESSING THE CUMULATIVE TOXIC EFFECTS POSED BY TWO OR MORE PESTICIDES THAT ARE TOXIC BY A COMMON MECHANISM.

To assess cumulative toxicity, EPA will characterize the total toxicity that can reasonably be expected to result from exposures to two or more pesticides that are toxic from a common mechanism. The potential for pesticide substances that have a common mechanism of toxicity to cause a cumulative effect(s) will be evaluated using a combined risk assessment. However, a prior assessment of the individual exposure patterns for chemicals within a common mechanism group will be performed to determine for which particular pesticides multiple exposures are likely. Hence, the Agency will assess cumulative toxicity and conduct combined risk assessments only on those substances that have a common mechanism of toxicity and for which aggregate exposures can reasonably be expected to occur. Overlapping of use patterns, frequency of use and application rates will be included as part of the exposure evaluation.

The nature of the cumulative toxicity will be characterized from consideration of: the toxic effect(s) caused by each substance; the duration and reversibility of the toxic effect(s); the pharmacokinetic properties of each substance; and known or reasonably plausible pharmacokinetic interactions among the substances. The potential for cumulative toxicity from pesticides whose toxic effects differ in site or nature but have a common etiology (e.g., pleiotropic effects of endocrine disruptors) will also be considered. In characterizing cumulative toxicity, certain assumptions will be made, unless data to the contrary are available. Toxic effects seen in animal studies will be assumed to occur in humans unless it is known that particular toxic effects observed in animals are not possible or otherwise do not occur in humans. (An example of a toxic effect that occurs in animals that EPA considers not relevant to human risk assessment is alpha-2u-globulin-induced nephropathy in male rats.) Concordance of site and nature of the effect between animals and humans will be assumed. Toxic effects that are common will be assumed to be cumulative, and the magnitude of the cumulation will be assumed to be additive. (Potency equivalencies will be determined for pesticides that cause a common toxic effect, and added together to determine the cumulative magnitude of the effect.)

As stated above, the characterization of cumulative toxicity of pesticides within a common mechanism group will also include consideration of the pharmacokinetics of each substance, pharmacokinetic interactions between substances, and the influence that pharmacokinetics may have on cumulative toxicity. An example of how the respective pharmacokinetics of two substances may interact to cause cumulative toxicity is as follows. A pesticide that contains a reactive functional group is found to

cause hepatotoxicity. The mechanism by which it causes hepatoxicity is alkylation of cellular proteins in hepatocytes, causing cellular death. Pharmacokinetic data show that the substance is excreted from the body via the kidney. A structurally analogous pesticide that contains the same reactive group and alkylates proteins similarly is found to cause nephrotoxicity and decreased renal function. Since the former pesticide is excreted through the kidney and the latter pesticide decreases renal function, it is conceivable that exposure to both pesticides could potentiate the hepatotoxicity of the former pesticide because it is not expected to be excreted as rapidly. A combined risk assessment of both pesticides would need to be conducted to characterize the likelihood of enhanced hepatotoxicity. A guidance document describing in more detail the policies and factors (including pharmacokinetic factors) EPA will consider when conducting combined risk assessments to assess cumulative toxicity, and how the factors will be used in such assessments, is in preparation and will be made available at a future date.

Upon completion of a combined risk assessment, the strengths, weaknesses and uncertainties of the assessment will be evaluated. These might include (but not limited to): availability of actual mechanistic data; mechanistic data that was inferred; gaps in available data; chemical specific toxicity that deviates from effects of the group; and discussions of interspecies variability in pharmacokinetics.